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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 05/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/743,813	RAMESH ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-89 and 91-95* is/are pending in the application.

4a) Of the above claim(s) *72-87* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *88,89 and 91-95* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12/24/03* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☑ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 12/2/06
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

An amendment was received and entered on 3/6/06.

Claim 90 was cancelled

Claims 72-89, and 91-95 remain pending.

Claims 72-87 stand withdrawn.

Claims 89 and 91-95 are under consideration in this Office Action.

Claim Objections

The objection to claims 88 and 95 is withdrawn because "luminal" is the more common spelling.

Rejections Withdrawn

The rejections of claims 88-95 under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (Cancer Res. 62: 3743-3750, 2002) in view of Heidrun et al (US Patent 5,789,244), and in view of Heidrun and Mullen et al (Oncologist 7:106-119, 2002), are withdrawn in view of Applicant's amendment deleting alkyl sulfates from the claims.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 88, 89, and 91-95 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of treating a superficial bladder tumor in the mucosal layer of the lumenal surface of a bladder by contacting the

lumenal surface of the bladder with a transduction enhancing agent according to formula I or II in claim 88, and subsequently or simultaneously contacting the tumor with an oncolytic virus, does not reasonably provide enablement for methods of treating bladder cancer in the muscular layer of the bladder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Claims 88-95 are directed to methods of treating cancer of the bladder by contacting the lumenal surface of the bladder with a composition comprising an oncolytic virus and a transduction enhancing agent that is sodium salt of a sulfate ester i.e. general formula I of claim 88, or a p-alkyl benzene sulfonate, i.e. general formula II.

The claims embrace any type of bladder cancer including superficial tumors and invasive cancers affecting the muscular layer of the bladder.

Mullen et al (Oncologist 7:106-119, 2002) taught that the concept of using oncolytic viruses in the treatment of cancer was recognized in the 1940s and 1950s. See page 106, paragraphs bridging columns 1 and 2. Sutton et al (Mol. Ther. 2(3): 211-217, 2000) taught non-replicative (non-oncolytic) adenovirus-mediated suicide gene therapy of orthotopic bladder cancer by direct administration to the tumor. See abstract. Cozzi et al (FASEB J. (March 5, 2001) 10.1096/fj.00-0533fje) taught intravesicular oncolytic viral therapy with an attenuated, replication-competent, herpes simplex virus in an orthotopic model. See entire document. Tumors were generated by intravesicular inoculation with tumor cells leading to superficial tumors accessible by lumenal delivery. See page 5, first paragraph.

Sutton (2000) also taught that administration of adenoviral vectors to the lumenal surface of the bladder resulted in transduction of only the most superficial layers of the bladder mucosa, and did not result in penetration to an intramuscular tumor. See abstract, and paragraph bridging columns 1 and 2 on page 214.

The instant specification showed that pretreatment of bladders with a p-alkyl benzene sulfonate surfactant led to adenoviral infection of essentially only the surface layer of cells. See Figs 30B. There is no evidence of viral penetration to the muscular layer.

The specification provided no guidance as to how to obtain oncolytic viral transduction of tumors located in the muscle of the bladder by contacting the lumenal surface of the bladder.

Thus one of skill in the art would not have reasonably expected to be able to use the claimed invention to treat bladder tumors other than superficial tumors located in the mucosal layer of the lumenal surface of the bladder. Due to the lack of guidance and examples in the specification, and the state of the art, one would have had to perform undue experimentation in order to practice the claimed method commensurate in scope with the claims, i.e. to treat tumors of the muscular layer of the bladder by administration of oncolytic viruses to the lumenal surface of the bladder.

Response to Arguments

Applicant's arguments filed 3/6/06 have been fully considered but they are not persuasive.

Applicant addresses the enablement rejection at pages 6 and 7. Applicant submits that one of skill in the art relying on the disclosure could practice the invention as claimed. This argument is unpersuasive because it is a statement of opinion that is not supported by evidence. The scope of the claims embraces treatment of superficial bladder cancer as well as tumors of the muscular layer beneath the bladder epithelium. As discussed above, the specification enables only treatment of superficial tumors. Applicant has not addressed the portion of the rejection that deals with this issue, and the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 88, 89, and 91-95 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Zhang et al (Cancer Res. 62: 3743-3750, 2002), in view of Heidrun et al (US Patent 5,789,244) and Gaffar et al (US Patent 5,368,844).

Zhang taught that adenovirus CG8840 was a urothelium-specific adenovirus variant that eliminates bladder tumors when administered at 3.33×10^9 pfu in combination with docetaxel. See abstract.

Zhang did not teach administration to the lumenal surface of the bladder, or the use of a transduction enhancing agent that was an sodium alkyl benzene sulfonate salt.

Heidrun taught methods of treating bladder cancer by intravesical administration of adenoviral vectors. See entire document, e.g. column 2, lines 32-46, and column 7, lines 13-21. Heidrun taught that adenoviral transduction of bladder tissue could be improved by disruption of the epithelial glycosaminoglycan layer by pretreatment of the bladder with a delivery enhancing agent such as sodium lauryl sulfate. See column 5, lines 16-28 and 36-41. Delivery enhancing agents were administered either with, or prior to, adenovirus. See column 6, lines 49-67. Heidrun also suggested adenovirus titres of as high as $5X\ 10^{10}$. See column 6, lines 50-55.

Gaffar taught that sodium lauryl sulfate and sodium dodecyl benzene sulfonate are anionic surfactants with similar performance characteristics. See column 12, line 61 to column 13, line 9.

It would have been obvious to of one of ordinary skill in the art at the time of the invention to modify the method Zhang by applying the adenovirus to the lumenal surface of a bladder, as taught by Heidrun, in order to treat bladder cancer. One would have been motivated to use the virus in vivo because this was the whole point of producing the virus (see last sentence of Zhang abstract). One would have been motivated to use lumenal delivery because this allows direct access to superficial tumors, and because Zhang points out that urethral access to bladder tumors (which leads to lumenal administration) makes bladder tumors appealing targets for viral therapy. It would have been similarly obvious to modify the method of Zhang by treating

mouse bladders with sodium lauryl sulfate or sodium dodecyl benzene sulfonate. One would have been motivated to do so to improve access to tumors in the bladder epithelium. The cited art suggests a range of virus concentrations overlapping the claimed lower limit, so the claimed concentration is prima facie obvious.

The combined references do not a pretreatment using 0.1 wt. % or less of a transduction enhancing agent. However, MPEP 2144.05 IIA indicates that differences in concentration generally will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case is clear that the concentration of the delivery-enhancing agent is a result effective variable that is routinely optimized because it can be delivered in a range from 1-50% v/v.

Claims 88, 89, and 91-95 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Watanabe et al (Int. J. Cancer 92: 712-717, 2001), in view of Heidrun et al (US Patent 5,789,244), Mullen et al (Oncologist 7:106-119, 2002), and Gaffar et al (US Patent 5,368,844).

Watanabe taught treatment of bladder cancer with replication deficient adenovirus carrying a suicide gene in an orthotopic mouse model of bladder cancer. The adenovirus carried a dominant negative version of *ras*, was instilled intravesically, and inhibited the growth of superficial tumors. 10^9 plaque forming units of adenovirus

were delivered. See abstract; page 714, column 1, paragraphs 2 and 3; page 715, column 1, first two full paragraphs; and Fig. 4 on page 715.

Watanabe did not teach an oncolytic virus, or the use of a transduction enhancing sodium alkyl benzene sulfonate salt.

Heidrun taught methods of treating bladder cancer by intravesical administration of adenoviral vectors. See entire document, e.g. column 2, lines 32-46, and column 7, lines 13-21.

Heidrun taught that adenoviral transduction of bladder tissue could be improved by disruption of the epithelial glycosaminoglycan layer by pretreatment of the bladder with a delivery enhancing agent such as sodium lauryl sulfate. See column 5, lines 16-28 and 36-41. Delivery enhancing agents were administered either with, or prior to, adenovirus. See column 6, lines 49-67. Heidrun also suggested adenovirus titres of as high as $5X\ 10^{10}$. See column 6, lines 50-55.

Gaffar taught that sodium lauryl sulfate and sodium dodecyl benzene sulfonate are anionic surfactants with similar performance characteristics. See column 12, line 61 to column 13, line 9.

Mullen taught that oncolytic viruses expressing therapeutic transgenes offered a distinct advantage over analogous replication deficient gene therapy vectors because the virus amplifies itself through several rounds of replication allowing a concomitant increase in transgene expression leading to an amplified antitumor effect. See page 108, column 1, first full paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Watanabe by treating the mouse bladders with sodium lauryl sulfate and to substitute replication competent adenoviruses for replication deficient ones. One would have been motivated to use sodium lauryl sulfate or sodium dodecyl benzene sulfonate to improve access to superficial tumors in the bladder epithelium by disrupting the glycosaminoglycan layer of the bladder epithelium, as taught by Heidrun. One would have been motivated to substitute an oncolytic virus for the replication deficient virus in order to take advantage of an amplified antitumor effect due to viral replication, as taught by Mullen. The cited art suggests a range of virus concentrations overlapping the claimed lower limit, so the claimed concentration is prima facie obvious.

The combined references do not teach a pretreatment using 0.1 wt. % or less of sodium dodecyl benzene sulfonate. However, MPEP 2144.05 IIA indicates that differences in concentration generally will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). In this case it is clear that the concentration of the delivery-enhancing agent is a result effective variable that is routinely optimized because it can be delivered in a range from 1-50% v/v.

Response to Arguments

Applicant's arguments filed 1/3/06 have been fully considered to the extent that they apply to the rejections set forth above but they are not persuasive.

The obviousness rejections of compositions and methods comprising a sodium alkyl benzene sulfonate salt are addressed at pages 10-11 of the response. Applicant asserts that one of skill in the art would not be motivated to combine a reference such as Gaffar with Zhang and Heidrun, and cold not have done so with a reasonable expectation of success. This is unpersuasive because it is only a statement of opinion and is not supported by evidence. One would have substituted the sodium dodecyl benzene sulfonate of Gaffar for the sodium lauryl sulfate of Heidrun because these anionic surfactants are structurally similar and Gaffer taught that they had similar performance characteristics. See column 12, line 61 to column 13, line 9. 2144.09 indicates that a prima facie case of obviousness may be made when chemical compounds have very close structural similarities and similar utilities, stating that "[a]n obviousness rejection based on similarity in chemical structure and function entails the motivation of one skilled in the art to make a claimed compound, in the expectation that compounds similar in structure will have similar properties." Because the use of surfactants, such as sodium lauryl sulfate, was well known in the prior art as evidenced by Heidrun, it would have been obvious to substitute any known anionic surfactant with similar performance characteristics for sodium lauryl sulfate. Because of the structural and functional similarities of these surfactants, one could have done so with a reasonable expectation of success. For these reasons the rejections are maintained.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 571-272-0762. The examiner can normally be reached Monday through Friday between the hours of 6:00 AM and 3:30 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Peter Paras, can be reached at (571) 272-4517. The official central fax number is 571-273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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